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(54) ESTER AND COMBINATIONS OF AN ORGANIC NITRATE AND A SALICYLATE

ESTER UND KOMBINATIONEN VON EINEM ORGANISCHEN NITRAT UND EINEM SALICYCLAT
ESTERS ET COMBINAISONS D'UN NITRATE ORGANIQUE ET D'UN SALICYLATE

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PT SE**

(56) References cited:
**EP-A-0 449 426 WO-A-92/01668
WO-A-92/16506**

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- EUR. HEART J. vol. 12 SUP.A , 1991 pages 2 - 4
C.R. CONTI 'Why use a nitrate in 1990?'
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aspirin on the hemodynamic effects of
sublingual nitroglycerin.'

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specification

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Description

The invention relates to pharmaceutical products.

The term "organic nitrates" as used in this specification refers to pharmacologically active organic nitrate compounds which relieve, or act as prophylactic against, angina pectoris.

Organic nitrates are dilators of arterial and venous smooth muscle. Their dilation action on the venous system increases the venous capacity allowing pooling of venous blood. This in turn reduces the volume of blood returning to the heart thereby lessening the strains on the heart muscle by reducing the pressure in the heart chambers (ventricles). This, in turn, reduces the oxygen requirements of the heart muscle. The dilation action on the arterial system is achieved by increasing the volume of the arterial system with consequent lower resistance to blood flow. This, in turn, reduces the work that the heart is required to do. In the coronary arteries (heart) a transient widening of the arteries (vasodilation) increases blood circulation to the heart muscle thereby increasing oxygen availability to the heart muscle.

Patients with coronary artery narrowing may suffer from angina pectoris which is usually brought on by exercise, emotion or eating. The organic nitrates by virtue of their action described above relieve the symptoms of angina pectoris.

In more detail, organic nitrates act in two ways - indirectly and directly.

Indirectly: they are smooth muscle relaxants and thus dilate both arterial and venous blood vessels. At lower doses their action is mainly on the venous system resulting in a decreased right and left ventricular filling pressure. At lower doses, however, they have little effect on the systemic (arterial) filling pressure. At higher doses, the arterial effects are more marked and decreased systemic resistance is accompanied by a reduction in blood pressure (Flaherty et al 1976). The venodilating and arterial effects of nitrates relieve ischaemia (the cause of angina, pain) by reducing determinates of myocardial oxygen demand.

Directly: they relieve ischaemia by direct action on the coronary vasculature thereby increasing intercoronary collateral flow and reversal of coronary artery spasm.

One widely used organic nitrate is isosorbide mononitrate (ISMN) which is an active metabolite of Isosorbide dinitrate (ISDN). ISMN has a high bioavailability and has a comparatively long half life (4-5 hours). Thus it is very suitable for prophylactic angina therapy. This is particularly so when it is presented as a sustained release formulation.

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The invention provides the use of a compound consisting of a salicylate of an esterifiable organic nitrate in the preparation of a medicament for the prophylaxis or treatment of angina and to achieve an anti-platelet effect.

The term "salicylate" refers to a salicylate or derivative or complex thereof having anti-platelet activity.

Preferably, the organic nitrate is directly esterifiable. In other words, the organic nitrate has an hydroxy group which is available for esterification.

The organic nitrate may be an isosorbide nitrate such as isosorbide 2-mononitrate or, most preferably isosorbide 5-mononitrate.

Alternatively, the organic nitrate is a glyceryl nitrate such as glyceryl trinitrate (also known as 1,2,3-Propanetriol trinitrate and Nitroglycerin).

Alternatively, the organic nitrate is a pentaerythritol nitrate such as pentaerythritol trinitrate (also known as Pentaerythritol trinitrol).

Alternatively, the organic nitrate may be indirectly esterifiable by removal of a nitrate from the nitrate compound and replacement by an hydroxy group prior to esterification.

In this case, the organic nitrate may be selected from the group consisting of Mannitol Hexanitrate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propatyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

According to the invention there are provided the salicylates of the above-mentioned nitrates and pharmaceutical compositions containing them.

In a particularly preferred embodiment of the invention the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

The product may be adapted for oral administration or percutaneous administration.

The invention also provides a tablet or capsule comprising a pharmaceutical product of the invention.

The invention further provides a transdermal patch including a pharmaceutical product of the invention.

The invention especially preferably provides the compound Isosorbide 5-mononitrate-2-aspirinate.

In another aspect the invention provides a process for preparing a pharmaceutical product of the invention which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

Prferably, the esterification is carried out using a coupling agent and/or a catalyst.

The coupling agent typically is a carbodiimide such as Dicyclohexylcarbodiimide (DCC).

The catalyst may comprise a pyridine derivative or paratoluene sulphonic acid.

Prferably, the esterification is carried out in nonaqueous conditions.

Typically, the process is carried out using methylenechloride as a solvent.

Preferably the process is carried out at a temperature below 5°C, most preferably at 0°C or below.

The invention will be more clearly understood from the following description thereof given by way of example only.

10

EXAMPLE 1

Synthesis of acetylsalicyloxyisosorbide mononitrate

15 Materials:

Acetylsalicylic acid

Isosorbide mononitrate

Dicyclohexylurea (DCC)

20

Dimethylaminopyridine (DMAP)

Dichloromethane (dry)

Citric acid solution (20%w/v in water)

Sodium bicarbonate aqueous solution saturated

25

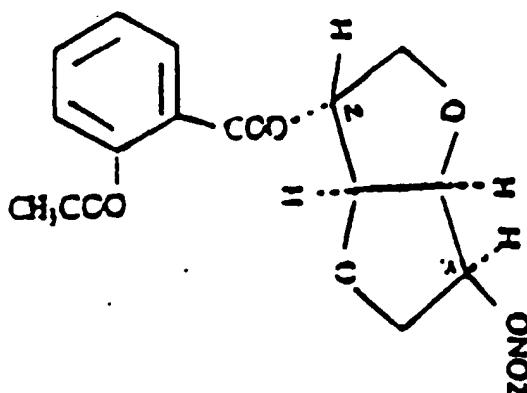
Sodium sulphate anhydrous

Method:

Add DMAP (0.03 gm) and isosorbide mononitrate (1.85gm, 0.01M) to a cold (0°C) and well stirred solution of acetylsalicylic acid (1.8gm, 0.01M) in dry dichloromethane (10ml). Gradually add DCC (2.06gm, 0.01M). Stir for 10 minutes at room temperature. Remove the precipitate by filtration. The filtered solution was washed with 2 x 25ml aliquots of cold 20% citric acid solution and then 2 x 25ml aliquots of saturated sodium bicarbonate solution. Dry the lower organic layer with anhydrous sodium sulphate filter and remove the solvent in vacuo. The product is purified on a sigel column using dichloromethane as eluent. The yield of the oily semisolid product was 50-75%.

The product has the following structure:

35



50

The product may be named as Isosorbide-5-mononitrate-2-aspirinate, or 2-[2-Acetoxybenzoyl]-isosorbide-5-mononitrate, or 2-Acetylsalicyloxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate.

Oil/low melting point solid	Molecular formula C ₁₅ H ₁₅ O ₉ N Molecular weight 353
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5 Infra red spectrum (thin film) 1780,1740,1640 cm⁻¹. The infra red analysis for isosorbide mononitrate is shown in Fig. 1. Fig. 2 is the infra red analysis for the product of the example.

Proton magnetic Resonance Spectrum See PMR BB-24 appended.

Thin Layer Chromatogram: Sigel GF 254/dichloromethane rf=0.8.

10 Mass spectrum (EI) MI 353

Because of the inherent lability of the starter and product ester groupings it is necessary to select mild reaction conditions. The general method of Neises, B and Steglich, W, Angew. Chem. Int Ed Eng. 17 (1978) No. 7, 522-524 was selected because of the mild reacting condition. The direct formation of acetylsalicyloxyisosorbide-5-mononitrate from acetylsalicylic acid and isosorbide - 5-mononitrate is accomplished by the use of the coupling reagent N,N1-dicyclohexylcarbodiimide (DCC). The particular virtue of this method lies in its suitability for acid sensitive substrates such as esters. The rate of reaction is greatly increased by addition of catalytic amounts of 4-dimethylaminopyridine. Pyridine or p-toluene sulphonic acid may also be used.

20 **Indirect Esterification**

Acid chlorides react with primary and secondary alcohols to give esters in good yield.

Anhydrides may also be used for the esterification of alcohols in the presence of a suitable catalyst. Acidic catalysts such as sulphuric acid or zinc chloride and basic catalysts such as pyridine are generally used.

25 **Direct Esterification**

Direct esterification procedures involving carboxylic acids and alcohols can be accomplished by the addition of concentrated sulphuric acid or dry HCl to the reaction mixture.

30 Various methods for the preparation of esters are described in "Comprehensive Organic Transformations" - A guide to functional group preparations by Richard C. Larock, VCH Publishers Inc 1989, especially pages 966-972, 978-979, 980-981, 985-987, 989-990.

As the product of Example 1 is an oil/low melting point solid, it is likely to be particularly suitable for percutaneous application, by means of a transdermal patch or for oral application in the form of a capsule, such as a soft gelatin capsule.

35 A widely used organic nitrate is Isosorbide Mono or di nitrate. Such agents act directly on the coronary arteries dilating them and thus improving the blood flow to the heart muscle and thus relieving the pain of angina pectoris. Another way that organic nitrates in general relieve the pain of angina is by reducing the requirements of the myocardium (heart muscle) for oxygen by reducing the volume of blood returning to the heart.

40 The pharmaceutical products of the invention are particularly for the prophylaxis of chronic stable angina pectoris. The invention provides a new combined prophylactic therapy which will deal with the pain of angina and decrease the risk of thrombosis leading to heart attack. Patients with angina pectoris have diseased coronary arteries. All patients with this degree of diseased coronary arteries are at increased risk of developing thrombosis (or clot).

In a particularly preferred embodiment of the invention the anti-platelet agent is ASPIRIN (acetylsalicylic acid).

45 Aspirin® has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agent. As such, it is a most useful drug. In more recent years, however, it has been discovered that aspirin has a powerful anti-platelet effect. Platelets are microscopic particles within the blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin prevents the sticking together of platelets and thus helps prevent the occurrence of heart attack or its complications.

50 The composition may be arranged for any desired release profile. The components may be released simultaneously or in some cases the organic nitrate is released more slowly than the Aspirin.

The effect of the pharmaceutical product of the invention is in the treatment of angina pectoris and in reducing the risk of developing myocardial infarction.

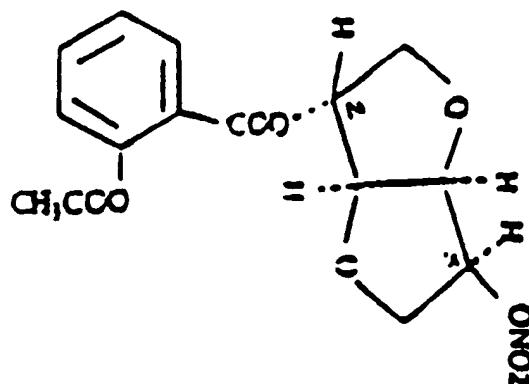
It is anticipated that, while the invention has been specifically described with reference to the combination of Iso-55 sorbid nitrate and Aspirin, it is expected that combination products of other known anti-angina agents are anti-platelet agents may also be used in combination.

Providing a nitrate and an anti platelet agent in a single dose pharmaceutical product has considerable advantages from a compliance viewpoint. If a patient is required to take a nitrate and aspirin separately there is a risk that one or

other will be forgotten. It is also quicker and easier for a doctor to prescribe such a combination product.

Claims

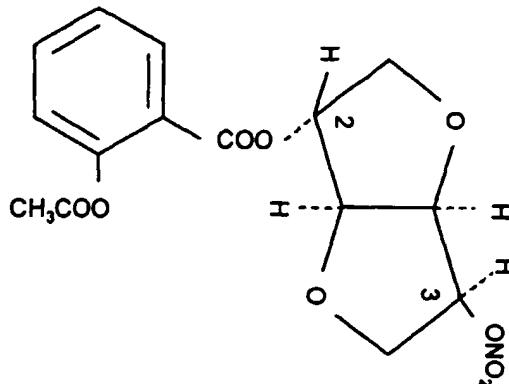
5. 1. A salicylate ester of an organic nitrate selected from an isosorbide nitrate, a glyceryl nitrate, a pentaerythritol nitrate, mannitolhexanitrate, trotnitrate phosphate, propatyl nitrate and clonitrate.
10. 2. A salicylate ester of an organic nitrate as claimed in claim 1 selected from glyceryl trinitrate, pentaerythritol trinitrate and pentaerythritol tetranitrate.
15. 3. A salicylate ester of an organic nitrate as claimed in claim 1 selected from isosorbide-2-mononitrate and isosorbide-5-mononitrate.
20. 4. A compound as claimed in any of claims 1 to 3 formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.
25. 5. A pharmaceutical composition, containing as the active ingredient a salicylate ester according to any of claims 1 to 4.
30. 6. A pharmaceutical composition as claimed in claim 5 which is adapted for oral administration.
35. 7. A pharmaceutical composition as claimed in claim 6 in the form of a tablet or capsule.
40. 8. A pharmaceutical composition as claimed in claim 5 which is adapted for percutaneous administration.
45. 9. A pharmaceutical composition as claimed in claim 8 in the form of a transdermal patch.
50. 10. A compound of the formula:



45. 11. A transdermal patch including a compound as claimed in claim 10
50. 12. A soft capsule including a compound as claimed in claim 10.
55. 13. The use of a compound consisting of a salicylate of an esterifiable organic nitrate according to claim 1 in the preparation of a medicament for the prophylaxis or treatment of angina and to achieve an anti-platelet effect.
60. 14. The use as claimed in claim 13 wherein the esterifiable organic nitrate is indirectly esterifiable.
65. 15. The use as claimed in claim 13 wherein the esterifiable organic nitrate is directly esterifiable.
70. 16. The use as claimed in any of claims 13 to 15 wherein the organic nitrate comprises a compound according to any of claims 1 to 4 or 10.

Patentansprüche

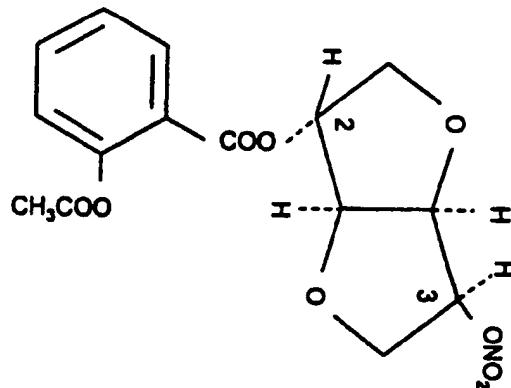
1. Salicylsäureester eines organischen Nitrates, das aus folgendem ausgewählt wird: Einem Isosorbidnitrat, inem Glyceronitrat, einem Pentaerythritnitrat, Mannitolhexanitrat, Trotnitratphosphat, Propatylnitrat und Clonitrat.
- 5 2. Salicylsäureester eines organischen Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Glyceroltrinitrat, Pentaerythrittrinitrat und Pentaerythrittetranitrat.
- 10 3. Salicylsäureester eines organischen Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Isosorbid-2-mononitrat und Isosorbid-5-mononitrat.
4. Verbindung nach einem der Ansprüche 1 bis 3, die durch Veresterung eines veresterbaren organischen Nitrates mit Acetylsalicylsäure gebildet wird.
- 15 5. Pharmazeutische Zusammensetzung, die als den aktiven Bestandteil einen Salicylsäureester nach einem der Ansprüche 1 bis 4 enthält.
6. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur oralen Verabreichung angepaßt wird.
- 20 7. Pharmazeutische Zusammensetzung nach Anspruch 6 in der Form einer Tablette oder Kapsel.
8. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur perkutanen Verabreichung angepaßt wird.
- 25 9. Pharmazeutische Zusammensetzung nach Anspruch 8 in der Form eines Transdermalpflasters.
10. Verbindung der Formel:



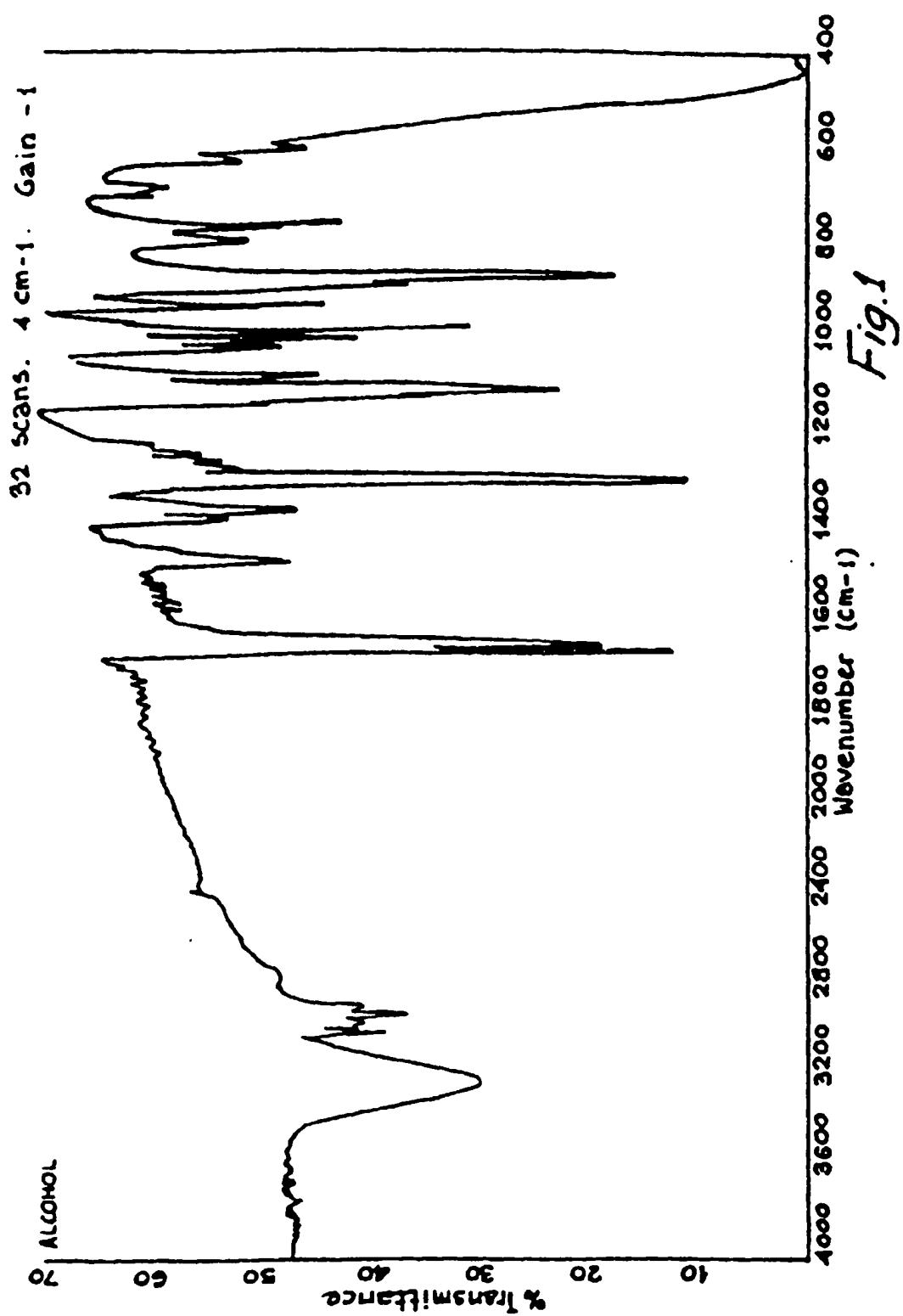
11. Transdermalpflaster, einschließlich einer Verbindung nach Anspruch 10.
- 45 12. Weichkapsel, einschließlich einer Verbindung nach Anspruch 10.
13. Verwendung einer Verbindung, die aus einem Salicylat eines veresterbaren organischen Nitrates nach Anspruch 1 bei der Herstellung eines Medikamentes für die Prophylaxe oder Behandlung von Angina und zur Erlangung einer Antithrombozytenwirkung besteht.
- 50 14. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat indirekt veresterbar ist.
15. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat direkt veresterbar ist.
- 55 16. Verwendung nach einem der Ansprüche 13 bis 15, worin das organische Nitrat eine Verbindung nach einem der Ansprüche 1 bis 4 oder 10 umfaßt.

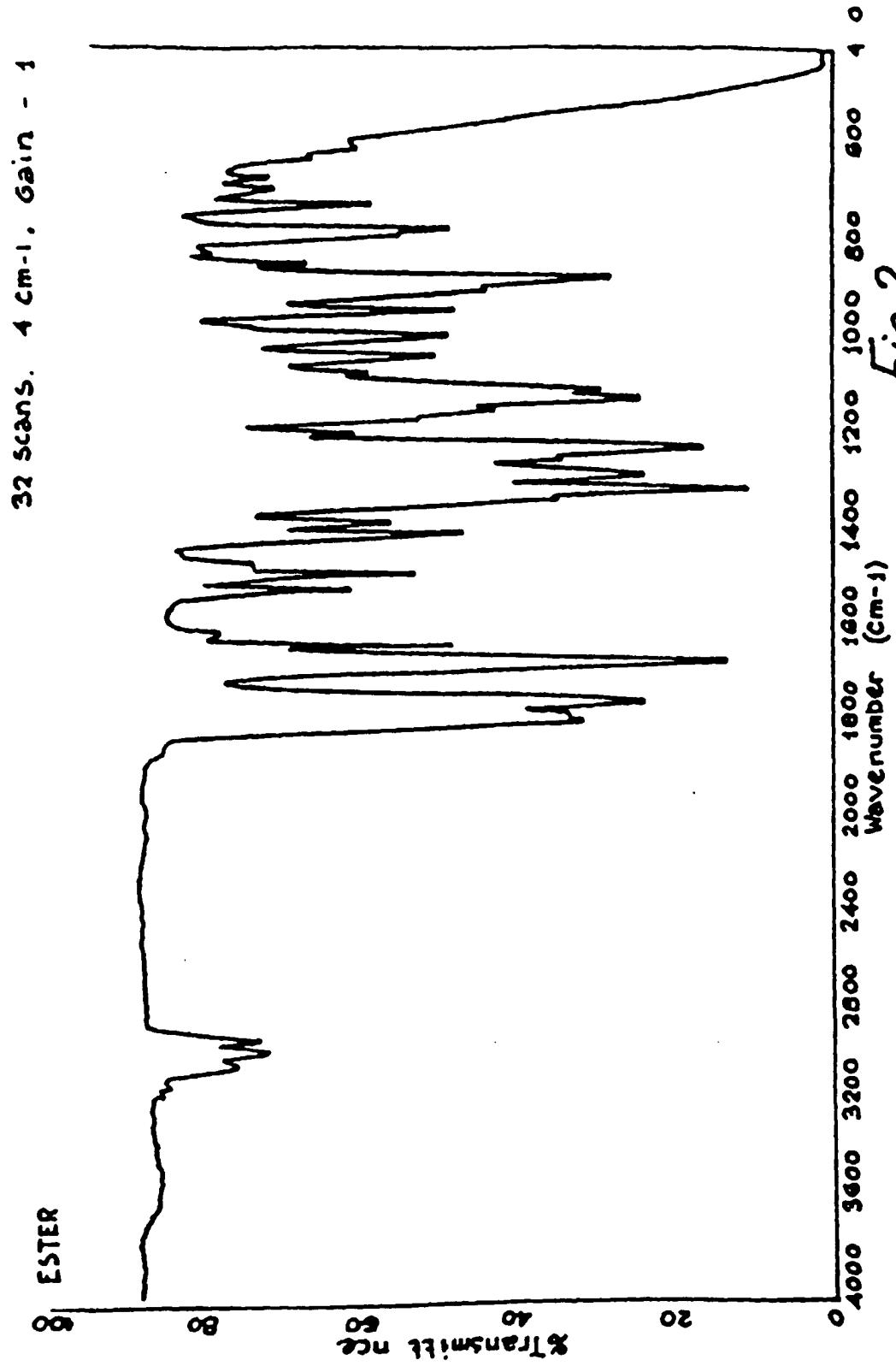
Revendications

1. Ester salicylate d'un nitrate organique choisi parmi un nitrate d'isosorbid , un nitrate de glycéryl , un nitrat de pentaérythritol, le mannitol xanitrat , le phosphate de trolnitrate, l nitrate de propatyle et le clonitrat .
- 5 2. Ester salicylate d'un nitrate organique s ion la revendication 1, choisi parmi le trinitrate de glycéryle, le trinitrat de pentaérythritol et le tétranitrate de pentaérythritol.
- 10 3. Ester salicylate d'un nitrate organique selon la revendication 1, choisi parmi l'isosorbide-2-mononitrate et l'isosorbide-5-mononitrate.
4. Composé selon l'une quelconque des revendications 1 à 3, formé par estérification d'un nitrate organique estérifiable avec de l'acide acétylsalicylique.
- 15 5. Composition pharmaceutique, contenant en tant que matière active un ester salicylate selon l'une quelconque des revendications 1 à 4.
6. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration orale.
- 20 7. Composition pharmaceutique selon la revendication 6, sous la forme d'un cachet ou d'une gélule.
8. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration percutanée.
9. Composition pharmaceutique selon la revendication 8, sous la forme d'un timbre transdermique.
- 25 10. Composé de formule :



11. Timbre transdermique comprenant un composé selon la revendication 10.
- 45 12. Gélule souple comprenant un composé selon la revendication 10.
13. Utilisation d'un composé constitué d'un salicylate d'un nitrate organique estérifiable selon la revendication 1 dans la préparation d'un médicament pour la prophylaxie ou le traitement de l'angine et pour obtenir un effet antiplaquettaire.
- 50 14. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable indirectement.
15. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable directement.
- 55 16. Utilisation selon l'un quelconque des revendications 13 à 15, dans laquelle le nitrate organique comprend un composé selon l'un quelconque des revendications 1 à 4 ou 10.







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45 Alternatively, the organic nitrate is a pentaerythritol nitrate such as pentaerythritol trinitrate (also known as Pentaerythritol trinitrol).

Alternatively, the organic nitrate may be indirectly esterifiable by removal of a nitrate from the nitrate compound and replacement by an hydroxy group prior to esterification.

In this case, the organic nitrate may be selected from the group consisting of Mannitol Hexanitrate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

50 According to the invention there are provided the salicylates of the above-mentioned nitrates and pharmaceutical compositions containing them.

In a particularly preferred embodiment of the invention the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

55 The product may be adapted for oral administration or percutaneous administration.

The invention also provides a tablet or capsule comprising a pharmaceutical product of the invention.

The invention further provides a transdermal patch including a pharmaceutical product of the invention.

The invention especially preferably provides the compound Isosorbide 5-mononitrate-2-aspirinate.

In another aspect the invention provides a process for preparing a pharmaceutical product of the invention which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

Preferably, the esterification is carried out using a coupling reagent and/or a catalyst.

The coupling agent typically is a carbodiimide such as Dicyclohexylcarbodiimide (DCC).

The catalyst may comprise a pyridine derivative or paratoluene sulphonic acid.

Preferably, the esterification is carried out in nonaqueous conditions.

Typically, the process is carried out using methylenechloride as a solvent.

Preferably the process is carried out at a temperature below 5°C, most preferably at 0°C or below.

The invention will be more clearly understood from the following description thereof given by way of example only.

10

EXAMPLE 1

Synthesis of acetylsalicyloxyisosorbide mononitrate

15 Materials:

Acetylsalicylic acid

Isosorbide mononitrate

Dicyclohexylurea (DCC)

20

Dimethylaminopyridine (DMAP)

Dichloromethane (dry)

Citric acid solution (20% w/v in water)

Sodium bicarbonate aqueous solution saturated

Sodium sulphate anhydrous

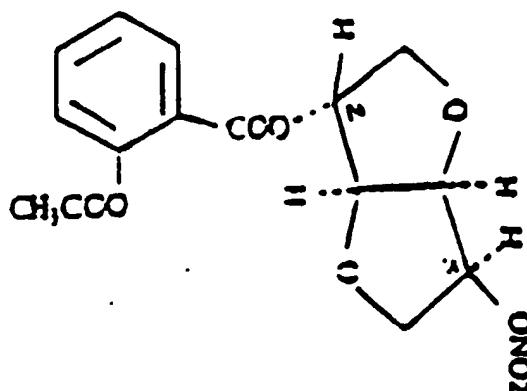
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Method:

Add DMAP (0.03 gm) and isosorbide mononitrate (1.85gm, 0.01M) to a cold (0°C) and well stirred solution of acetylsalicylic acid (1.8gm, 0.01M) in dry dichloromethane (10ml). Gradually add DCC (2.06gm, 0.01M). Stir for 10 minutes at room temperature. Remove the precipitate by filtration. The filtered solution was washed with 2 x 25ml aliquots of cold 20% citric acid solution and then 2 x 25ml aliquots of saturated sodium bicarbonate solution. Dry the lower organic layer with anhydrous sodium sulphate filter and remove the solvent in vacuo. The product is purified on a sigel column using dichloromethane as eluent. The yield of the oily semisolid product was 50-75%.

The product has the following structure:

35



50

The product may be named as Isosorbide-5-mononitrate-2-aspirinate, or 2-[2-Acetoxybenzoyl]-isosorbide-5-mononitrate, or 2-Acetylsalicyloxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate.

Oil/low melting point solid	Molecular formula C ₁₅ H ₁₅ O ₉ N Molecular weight 353
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5 Infra red spectrum (thin film) 1780,1740,1640 cm⁻¹. The infra red analysis for isosorbide mononitrate is shown in Fig. 1. Fig. 2 is the infra red analysis for the product of the example.

Proton magnetic Resonance Spectrum See PMR BB-24 appended.

Thin Layer Chromatogram: Sigel GF 254/dichloromethane rf=0.8.

10 Mass spectrum (EI) MI 353

Because of the inherent lability of the starter and product ester groupings it is necessary to select mild reaction conditions. The general method of Neises, B and Steglich, W, Angew. Chem. Int Ed Eng. 17 (1978) No. 7, 522-524 was selected because of the mild reacting condition. The direct formation of acetylsalicyloxyisosorbide-5-mononitrate from acetylsalicylic acid and isosorbide - 5-mononitrate is accomplished by the use of the coupling reagent N,N1-di-cyclohexylcarbodiimide (DCC). The particular virtue of this method lies in its suitability for acid sensitive substrates such as esters. The rate of reaction is greatly increased by addition of catalytic amounts of 4-dimethylaminopyridine. Pyridine or p-toluene sulphonic acid may also be used.

20 **Indirect Esterification**

Acid chlorides react with primary and secondary alcohols to give esters in good yield.

Anhydrides may also be used for the esterification of alcohols in the presence of a suitable catalyst. Acidic catalysts such as sulphuric acid or zinc chloride and basic catalysts such as pyridine are generally used.

25 **Direct Esterification**

Direct esterification procedures involving carboxylic acids and alcohols can be accomplished by the addition of concentrated sulphuric acid or dry HCl to the reaction mixture.

30 Various methods for the preparation of esters are described in "Comprehensive Organic Transformations" - A guide to functional group preparations by Richard C. Larock, VCH Publishers Inc 1989, especially pages 966-972, 978-979, 980-981, 985-987, 989-990.

As the product of Example 1 is an oil/low melting point solid, it is likely to be particularly suitable for percutaneous application, by means of a transdermal patch or for oral application in the form of a capsule, such as a soft gelatin capsule.

35 A widely used organic nitrate is Isosorbide Mono or di nitrate. Such agents act directly on the coronary arteries dilating them and thus improving the blood flow to the heart muscle and thus relieving the pain of angina pectoris. Another way that organic nitrates in general relieve the pain of angina is by reducing the requirements of the myocardium (heart muscle) for oxygen by reducing the volume of blood returning to the heart.

40 The pharmaceutical products of the invention are particularly for the prophylaxis of chronic stable angina pectoris. The invention provides a new combined prophylactic therapy which will deal with the pain of angina and decrease the risk of thrombosis leading to heart attack. Patients with angina pectoris have diseased coronary arteries. All patients with this degree of diseased coronary arteries are at increased risk of developing thrombosis (or clot).

In a particularly preferred embodiment of the invention the anti-platelet agent is ASPIRIN (acetylsalicylic acid).

45 Aspirin® has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agent. As such, it is a most useful drug. In more recent years, however, it has been discovered that aspirin has a powerful anti-platelet effect. Platelets are microscopic particles within the blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin prevents the sticking together of platelets and thus helps prevent the occurrence of heart attack or its complications.

50 The composition may be arranged for any desired release profile. The components may be released simultaneously or in some cases the organic nitrate is released more slowly than the Aspirin.

The effect of the pharmaceutical product of the invention is in the treatment of angina pectoris and in reducing the risk of developing myocardial infarction.

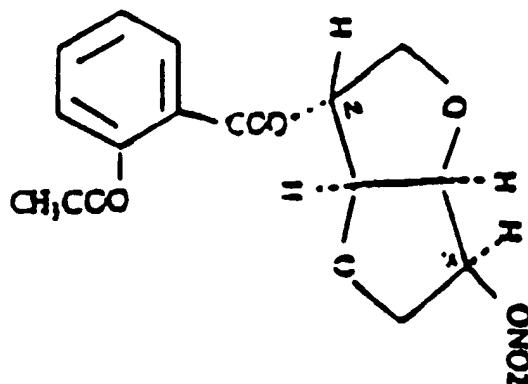
It is anticipated that, while the invention has been specifically described with reference to the combination of Iso-55 sorbid nitrate and Aspirin, it is expected that combination products of other known anti-angina agents are anti-platelet agents may also be used in combination.

Providing a nitrate and an anti platelet agent in a single dosage pharmaceutical product has considerable advantages from a compliance viewpoint. If a patient is required to take a nitrate and aspirin separately there is a risk that one or

other will be forgotten. It is also quicker and easier for a doctor to prescribe such a combination product.

Claims

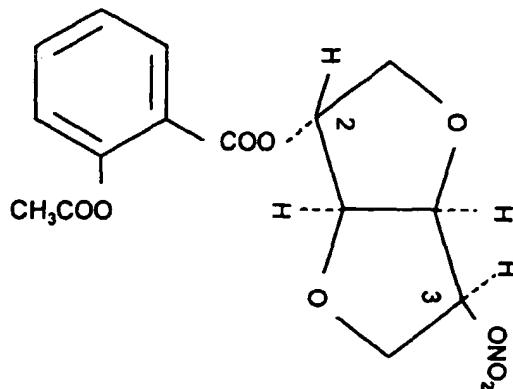
- 5 1. A salicylate ester of an organic nitrate selected from an isosorbide nitrate, a glyceryl nitrate, a pentaerythritol nitrate, mannitolhexanitrate, trotnitrate phosphate, propatyl nitrate and clonitrate.
- 10 2. A salicylate ester of an organic nitrate as claimed in claim 1 selected from glyceryl trinitrate, pentaerythritol trinitrate and pentaerythritol tetranitrate.
- 15 3. A salicylate ester of an organic nitrate as claimed in claim 1 selected from isosorbide-2-mononitrate and isosorbide-5-mononitrate.
4. A compound as claimed in any of claims 1 to 3 formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.
- 20 5. A pharmaceutical composition, containing as the active ingredient a salicylate ester according to any of claims 1 to 4.
6. A pharmaceutical composition as claimed in claim 5 which is adapted for oral administration.
7. A pharmaceutical composition as claimed in claim 6 in the form of a tablet or capsule.
- 25 8. A pharmaceutical composition as claimed in claim 5 which is adapted for percutaneous administration.
9. A pharmaceutical composition as claimed in claim 8 in the form of a transdermal patch.
10. A compound of the formula:



- 35 11. A transdermal patch including a compound as claimed in claim 10
- 40 12. A soft capsule including a compound as claimed in claim 10.
- 45 13. The use of a compound consisting of a salicylate of an esterifiable organic nitrate according to claim 1 in the preparation of a medicament for the prophylaxis or treatment of angina and to achieve an anti-platelet effect.
- 50 14. The use as claimed in claim 13 wherein the esterifiable organic nitrate is indirectly esterifiable.
- 55 15. The use as claimed in claim 13 wherein the esterifiable organic nitrate is directly esterifiable.
16. The use as claimed in any of claims 13 to 15 wherein the organic nitrate comprises a compound according to any of claims 1 to 4 or 10.

Patentansprüche

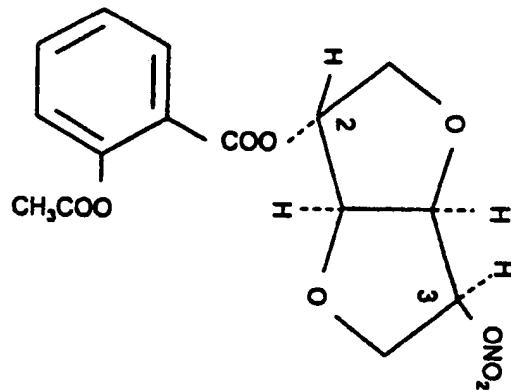
1. Salicylsäureester eines organischen Nitrates, das aus folgendem ausgewählt wird: Einem Isosorbidnitrat, einem Glyceronitrat, einem Penterythritnitrat, Mannitolxanitrat, Trohnitratphosphat, Propatrinitrat und Clonitrat.
- 5 2. Salicylsäureester eines organisch-n Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Glyceroltrinitrat, Penterythrittrinitrat und Penterythrittetranitrat.
- 10 3. Salicylsäureester eines organischen Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Isosorbid-2-mononitrat und Isosorbid-5-mononitrat.
4. Verbindung nach einem der Ansprüche 1 bis 3, die durch Veresterung eines veresterbaren organischen Nitrates mit Acetylsalicylsäure gebildet wird.
- 15 5. Pharmazeutische Zusammensetzung, die als den aktiven Bestandteil einen Salicylsäureester nach einem der Ansprüche 1 bis 4 enthält.
6. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur oralen Verabreichung angepaßt wird.
- 20 7. Pharmazeutische Zusammensetzung nach Anspruch 6 in der Form einer Tablette oder Kapsel.
8. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur perkutanen Verabreichung angepaßt wird.
9. Pharmazeutische Zusammensetzung nach Anspruch 8 in der Form eines Transdermalpflasters.
- 25 10. Verbindung der Formel:



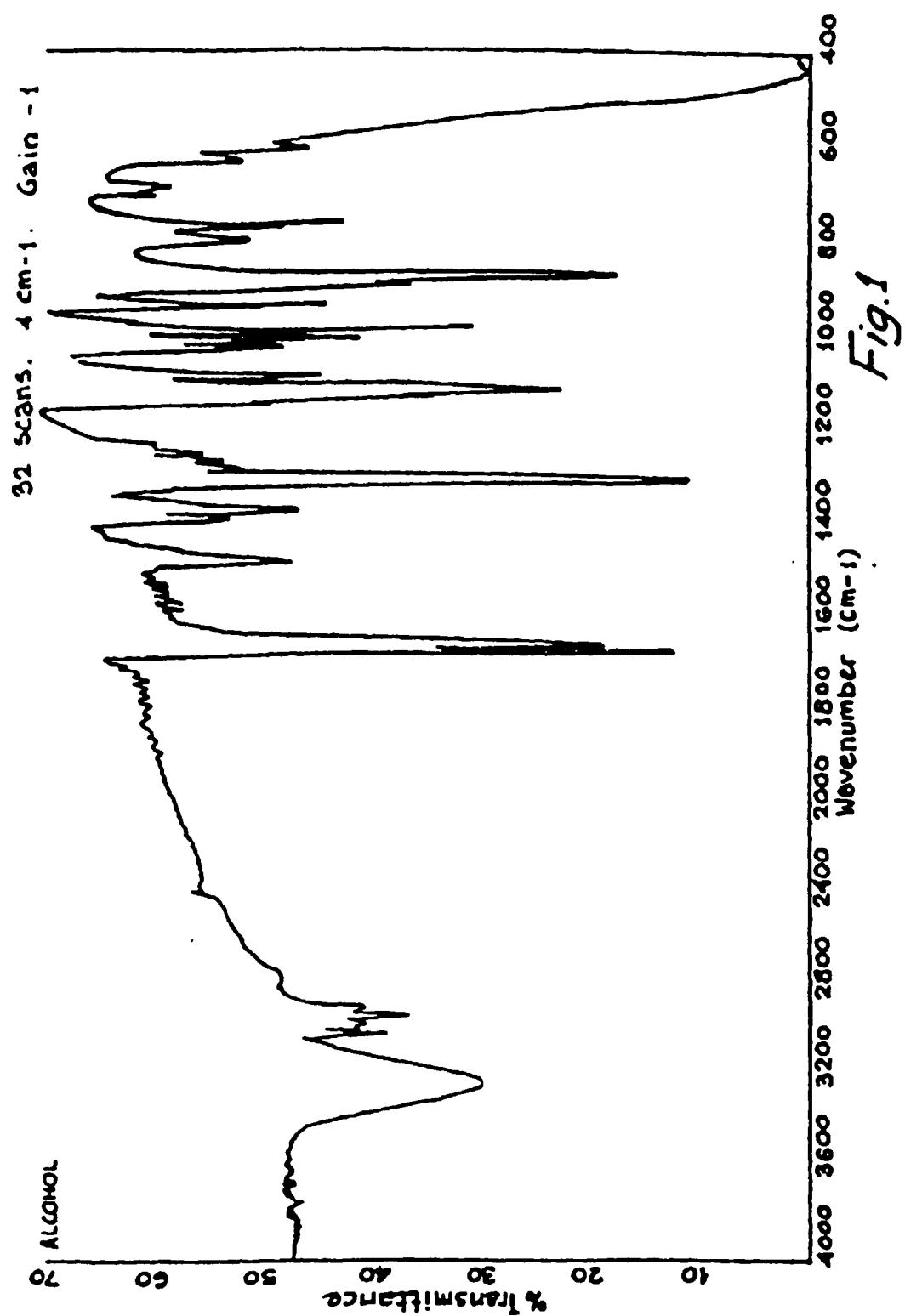
11. Transdermalpflaster, einschließlich einer Verbindung nach Anspruch 10.
- 45 12. Weichkapsel, einschließlich einer Verbindung nach Anspruch 10.
13. Verwendung einer Verbindung, die aus einem Salicylat eines veresterbaren organischen Nitrates nach Anspruch 1 bei der Herstellung eines Medikamentes für die Prophylaxe oder Behandlung von Angina und zur Erlangung einer Antithrombozytenwirkung besteht.
- 50 14. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat indirekt veresterbar ist.
15. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat direkt veresterbar ist.
- 55 16. Verwendung nach einem der Ansprüche 13 bis 15, worin das organische Nitrat eine Verbindung nach einem der Ansprüche 1 bis 4 oder 10 umfaßt.

Revendications

1. Ester salicylate d'un nitrate organique choisi parmi un nitrate d'isosorbid , un nitrate de glycéryl , un nitrate de pentaérythritol, le mannitolhexanitrate, le phosphate de trolnitrate, le nitrate de propatyle et le clonitrate.
- 5 2. Ester salicylate d'un nitrate organique selon la revendication 1, choisi parmi l trinitrate de glycéryle, la trinitrat de pentaérythritol et le tétranitrate de pentaérythritol.
- 10 3. Ester salicylate d'un nitrate organique selon la revendication 1, choisi parmi l'isosorbide-2-mononitrate et l'isosorbide-5-mononitrate.
4. Composé selon l'une quelconque des revendications 1 à 3, formé par estérification d'un nitrate organique estérifiable avec de l'acide acétylsalicylique.
- 15 5. Composition pharmaceutique, contenant en tant que matière active un ester salicylate selon l'une quelconque des revendications 1 à 4.
6. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration orale.
- 20 7. Composition pharmaceutique selon la revendication 6, sous la forme d'un cachet ou d'une gélule.
8. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration percutanée.
9. Composition pharmaceutique selon la revendication 8, sous la forme d'un timbre transdermique.
- 25 10. Composé de formule :



11. Timbre transdermique comprenant un composé selon la revendication 10.
- 45 12. Gélule souple comprenant un composé selon la revendication 10.
13. Utilisation d'un composé constitué d'un salicylate d'un nitrate organique estérifiable selon la revendication 1 dans la préparation d'un médicament pour la prophylaxie ou le traitement de l'angine et pour obtenir un effet antiplaquettaire.
- 50 14. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable indirectement.
15. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable directement.
- 55 16. Utilisation selon l'un quelconque des revendications 13 à 15, dans laquelle le nitrate organique comprend un composé selon l'une quelconque des revendications 1 à 4 ou 10.



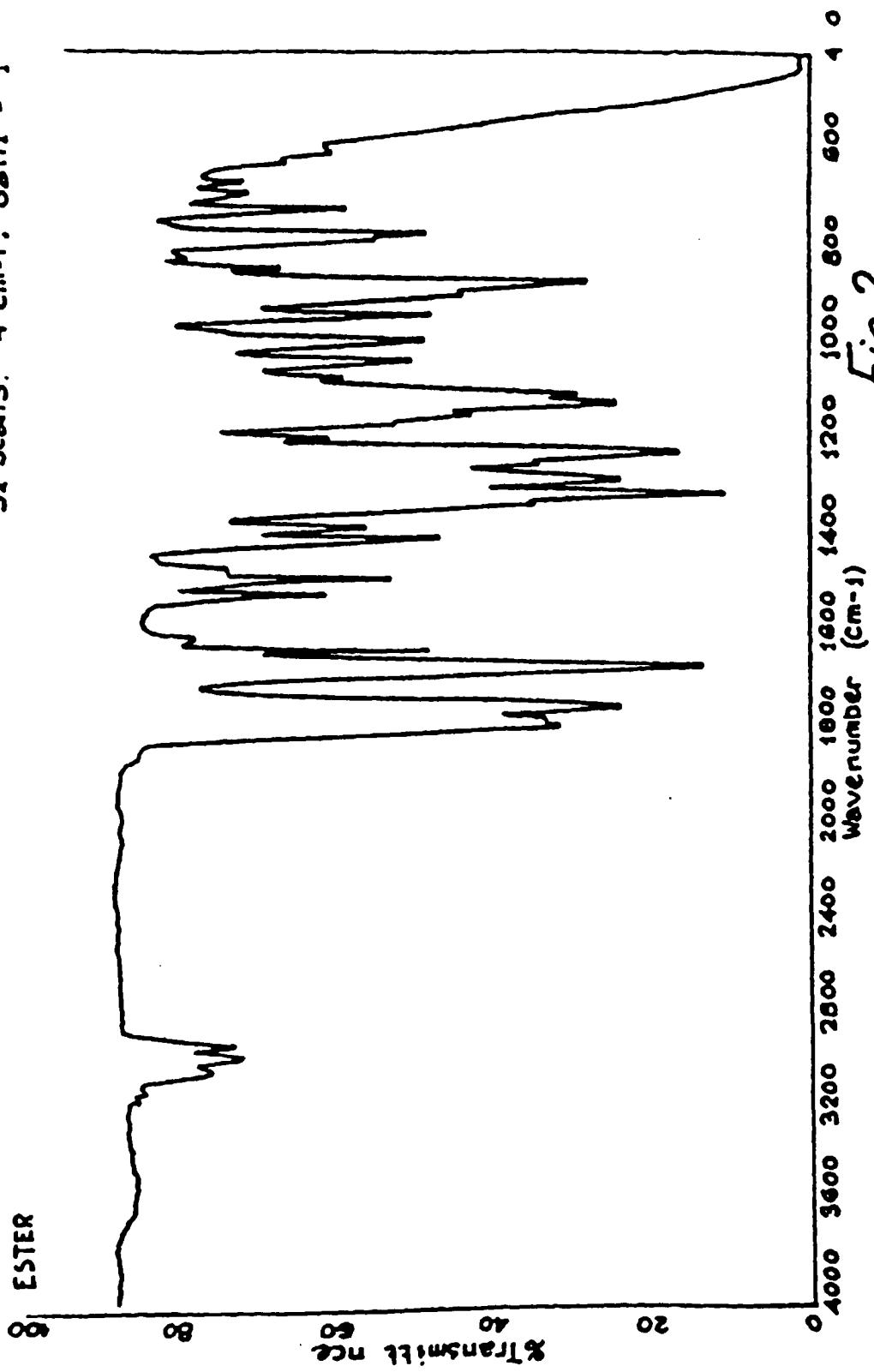
32 scans. 4 cm⁻¹. Gain - 1

Fig. 2



(19)

Europäisches Patentamt

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C07D 493/04, A61K 31/62,
A61K 31/625, A61K 31/60
// (A61K31/60, 31:21),
(A61K31/60, 31:34)**

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(54) ESTER AND COMBINATIONS OF AN ORGANIC NITRATE AND A SALICYLATE

ESTER UND KOMBINATIONEN VON EINEM ORGANISCHEN NITRAT UND EINEM SALICYCLAT
ESTERS ET COMBINAISONS D'UN NITRATE ORGANIQUE ET D'UN SALICYLATE

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL
PT SE**

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(43) Date of publication of application:
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(60) Divisional application: **95201369.6 / 0 676 204**

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**EP-A- 0 449 426 WO-A-92/01668
WO-A-92/16506**

- EUR. HEART J. vol. 12 SUP.A , 1991 pages 2 - 4
C.R. CONTI 'Why use a nitrate in 1990?'
- EUR. HEART J. vol. 9 SUP. A , 1988 pages 45 - 49
R. DE CATERINA 'Mechanisms for the in vivo
antiplatelet effects of isosorbide dinitrate.'
- EUR. J. CLIN. PHARMACOL. vol. 25 , 1983 pages
779 - 782 E. REY 'Pharmacological interaction
between nitroglycerin and aspirin after acute
and chronic aspirin treatment of healthy
subjects.'
- J. CARDIOVASC. PHARMACOL. vol. 5, no. 5 ,
1983 pages 874 - 877 S. WEBER 'Influence of
aspirin on the hemodynamic effects of
sublingual nitroglycerin.'

Remarks:

- Divisional application 95201369.6 filed on
26/07/93.
- The file contains technical information submitted
after the application was filed and not included in this
specification

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reason d statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

The invention relates to pharmaceutical products.

5 The term "organic nitrates" as used in this specification refers to pharmacologically active organic nitrate compounds which relieve, or act as prophylactic against, angina pectoris.

10 Organic nitrates are dilators of arterial and venous smooth muscle. The dilation action on the venous system increases the venous capacity allowing pooling of venous blood. This in turn reduces the volume of blood returning to the heart thereby lessening the strains on the heart muscle by reducing the pressure in the heart chambers (ventricles). This, in turn, reduces the oxygen requirements of the heart muscle. The dilation action on the arterial system is achieved by increasing the volume of the arterial system with consequent lower resistance to blood flow. This, in turn, reduces the work that the heart is required to do. In the coronary arteries (heart) a transient widening of the arteries (vasodilation) increases blood circulation to the heart muscle thereby increasing oxygen availability to the heart muscle.

15 Patients with coronary artery narrowing may suffer from angina pectoris which is usually brought on by exercise, emotion or eating. The organic nitrates by virtue of their action described above relieve the symptoms of angina pectoris.

20 In more detail, organic nitrates act in two ways - indirectly and directly.

Indirectly: they are smooth muscle relaxants and thus dilate both arterial and venous blood vessels. At lower doses their action is mainly on the venous system resulting in a decreased right and left ventricular filling pressure. At lower doses, however, they have little effect on the systemic (arterial) filling pressure. At higher doses, the arterial effects are more marked and decreased systemic resistance is accompanied by a reduction in blood pressure (Flaherty et al 25 1976). The venodilating and arterial effects of nitrates relieve ischaemia (the cause of angina, pain) by reducing determinates of myocardial oxygen demand.

25 Directly: they relieve ischaemia by direct action on the coronary vasculature thereby increasing intercoronary collateral flow and reversal of coronary artery spasm.

One widely used organic nitrate is isosorbide mononitrate (ISMN) which is an active metabolite of Isosorbide dinitrate (ISDN). ISMN has a high bioavailability and has a comparatively long half life (4-5 hours). Thus it is very suitable for prophylactic angina therapy. This is particularly so when it is presented as a sustained release formulation.

WO-A-92/01668 describes benzoic acid substituted derivatives having cardiovascular activity.

WO-A-92/16506 describes isoindoles having cardiovascular activity.

30 Eur. Heart J. Vol. 12 Sup, 1991, p. 2-4 refers to the beneficial usage of nitrates.

Eur. Heart J. Vol. 9 Sup. A, 1988, p. 45-49 refers to mechanisms for in vivo anti-platelet effects of isosorbide dinitrate.

Eur. J. Clin. Pharm. Vol. 25 1983, p. 779-782 refers to the pharmacological interaction between nitroglycerin and Aspirin after acute and chronic Aspirin treatment.

35 J. Cardiovasc. Pharm. Vol. 5, No. 5, 1983, p. 874-877 refers to the influence of Aspirin on the hemodynamic effects of sublingual nitroglycerin.

The invention provides the use of a compound consisting of a salicylate of an esterifiable organic nitrate in the preparation of a medicament for the prophylaxis or treatment of angina and to achieve an anti-platelet effect.

The term "salicylate" refers to a salicylate or derivative or complex thereof having anti-platelet activity.

40 Preferably, the organic nitrate is directly esterifiable. In other words, the organic nitrate has an hydroxy group which is available for esterification.

The organic nitrate may be an isosorbide nitrate such as isosorbide 2-mononitrate or, most preferably isosorbide 5-mononitrate.

45 Alternatively, the organic nitrate is a glyceryl nitrate such as glyceryl trinitrate (also known as 1,2,3-Propanetriol trinitrate and Nitroglycerin).

Alternatively, the organic nitrate is a pentaerythritol nitrate such as pentaerythritol trinitrate (also known as Pentaerythritol trinitrol).

50 Alternatively, the organic nitrate may be indirectly esterifiable by removal of a nitrate from the nitrate compound and replacement by an hydroxy group prior to esterification.

In this case, the organic nitrate may be selected from the group consisting of Mannitol Hexanitrate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

According to the invention there are provided the salicylates of the above-mentioned nitrates and pharmaceutical compositions containing them.

55 In a particularly preferred embodiment of the invention the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

The product may be adapted for oral administration or percutaneous administration.

The invention also provides a tablet or capsule comprising a pharmaceutical product of the invention.

The invention further provides a transdermal patch including a pharmaceutical product of the invention.

The invention especially preferably provides the compound Isosorbide 5-mononitrate-2-aspirinate.

In another aspect the invention provides a process for preparing a pharmaceutical product of the invention which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

Preferably, the esterification is carried out using a coupling reagent and/or a catalyst.

The coupling agent typically is a carbodiimide such as Dicyclohexylcarbodiimide (DCC).

The catalyst may comprise a pyridine derivative or paratoluene sulphonic acid.

Preferably, the esterification is carried out in nonaqueous conditions.

Typically, the process is carried out using methylenechloride as a solvent.

Preferably the process is carried out at a temperature below 5°C, most preferably at 0°C or below.

The invention will be more clearly understood from the following description thereof given by way of example only.

10

EXAMPLE 1

Synthesis of acetylsalicyloxyisosorbide mononitrate

15 Materials:

Acetylsalicylic acid

Isosorbide mononitrate

Dicyclohexylurea (DCC)

20

Dimethylaminopyridine (DMAP)

Dichloromethane (dry)

Citric acid solution (20% w/v in water)

Sodium bicarbonate aqueous solution saturated

Sodium sulphate anhydrous

25

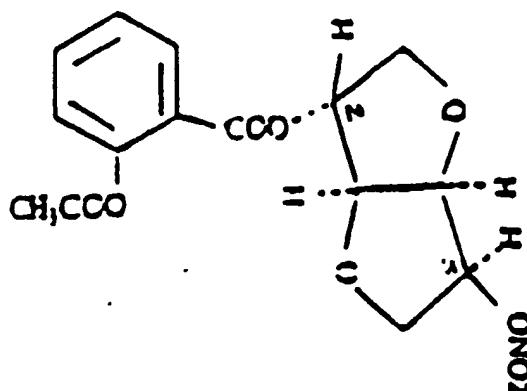
Method:

30

Add DMAP (0.03 gm) and isosorbide mononitrate (1.85gm, 0.01M) to a cold (0°C) and well stirred solution of acetylsalicylic acid (1.8gm, 0.01M) in dry dichloromethane (10ml). Gradually add DCC (2.06gm, 0.01M). Stir for 10 minutes at room temperature. Remove the precipitate by filtration. The filtered solution was washed with 2 x 25ml aliquots of cold 20% citric acid solution and then 2 x 25ml aliquots of saturated sodium bicarbonate solution. Dry the lower organic layer with anhydrous sodium sulphate filter and remove the solvent in vacuo. The product is purified on a sigel column using dichloromethane as eluent. The yield of the oily semisolid product was 50-75%.

The product has the following structure:

35



50

The product may be named as Isosorbide-5-mononitrate-2-aspirinate, or 2-[2-Acetoxybenzoyl]-isosorbide-5-mononitrate, or 2-Acetylsalicyloxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate.

Oil/low melting point solid	Molecular formula C ₁₅ H ₁₅ O ₉ N Molecular weight 353
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5 Infra red spectrum (thin film) 1780,1740,1640 cm⁻¹. The infra red analysis for isosorbide mononitrate is shown in Fig. 1. Fig. 2 is the infra red analysis for the product of the example.

Proton magnetic Resonance Spectrum See PMR BB-24 appended.

Thin Layer Chromatogram: Sigel GF 254/dichloromethane *r*f=0.8.

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Because of the inherent lability of the starter and product ester groupings it is necessary to select mild reaction conditions. The general method of Neises, B and Steglich, W, Angew. Chem. Int Ed Eng. 17 (1978) No. 7, 522-524 was selected because of the mild reacting condition. The direct formation of acetyl salicyloxy isosorbide-5-mononitrate from acetyl salicylic acid and isosorbide - 5-mononitrate is accomplished by the use of the coupling reagent N,N1-di-cyclohexylcarbodiimide (DCC). The particular virtue of this method lies in its suitability for acid sensitive substrates such as esters. The rate of reaction is greatly increased by addition of catalytic amounts of 4-dimethylaminopyridine. Pyridine or p-toluene sulphonic acid may also be used.

20 Indirect Esterification

Acid chlorides react with primary and secondary alcohols to give esters in good yield.

Anhydrides may also be used for the esterification of alcohols in the presence of a suitable catalyst. Acidic catalysts such as sulphuric acid or zinc chloride and basic catalysts such as pyridine are generally used.

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Direct esterification procedures involving carboxylic acids and alcohols can be accomplished by the addition of concentrated sulphuric acid or dry HCl to the reaction mixture.

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As the product of Example 1 is an oil/low melting point solid, it is likely to be particularly suitable for percutaneous application, by means of a transdermal patch or for oral application in the form of a capsule, such as a soft gelatin capsule.

35 A widely used organic nitrate is Isosorbide Mono or di nitrate. Such agents act directly on the coronary arteries dilating them and thus improving the blood flow to the heart muscle and thus relieving the pain of angina pectoris. Another way that organic nitrates in general relieve the pain of angina is by reducing the requirements of the myocardium (heart muscle) for oxygen by reducing the volume of blood returning to the heart.

40 The pharmaceutical products of the invention are particularly for the prophylaxis of chronic stable angina pectoris. The invention provides a new combined prophylactic therapy which will deal with the pain of angina and decrease the risk of thrombosis leading to heart attack. Patients with angina pectoris have diseased coronary arteries. All patients with this degree of diseased coronary arteries are at increased risk of developing thrombosis (or clot).

In a particularly preferred embodiment of the invention the anti-platelet agent is ASPIRIN (acetyl salicylic acid).

45 Aspirin® has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agent. As such, it is a most useful drug. In more recent years, however, it has been discovered that aspirin has a powerful anti-platelet effect. Platelets are microscopic particles within the blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin prevents the sticking together of platelets and thus helps prevent the occurrence of heart attack or its complications.

50 The composition may be arranged for any desired release profile. The components may be released simultaneously or in some cases the organic nitrate is released more slowly than the Aspirin.

The effect of the pharmaceutical product of the invention is in the treatment of angina pectoris and in reducing the risk of developing myocardial infarction.

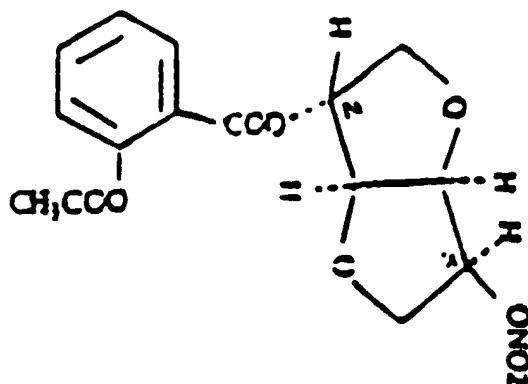
It is anticipated that, while the invention has been specifically described with reference to the combination of Iso-55 sorbid nitrat and Aspirin, it is expected that combination products of other known anti-angina ag nts are anti-platelet agents may also b used in combination.

Providing a nitrate and an anti platelet agent in a single dose pharmaceutical product has considerable advantages from a compliance viewpoint. If a patient is required to take a nitrate and aspirin s parat ly there is a risk that one or

other will b forgotten. It is also quicker and easier for a doctor to prescribe such a combination product.

Claim

- 5 1. A salicylate ester of an organic nitrate selected from an isosorbide nitrate, a glyceryl nitrat , a pentaerythritol nitrate, mannitolhexanitrate, trolnitrate phosphate, propatyl nitrate and clonitrate.
- 10 2. A salicylate ester of an organic nitrate as claimed in claim 1 selected from glyceryl trinitrate, pentaerythritol trinitrate and pentaerythritol tetranitrate.
- 15 3. A salicylate ester of an organic nitrate as claimed in claim 1 selected from isosorbide-2-mononitrate and isosorbide-5-mononitrate.
- 20 4. A compound as claimed in any of claims 1 to 3 formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.
- 25 5. A pharmaceutical composition, containing as the active ingredient a salicylate ester according to any of claims 1 to 4.
- 30 6. A pharmaceutical composition as claimed in claim 5 which is adapted for oral administration.
- 35 7. A pharmaceutical composition as claimed in claim 6 in the form of a tablet or capsule.
- 40 8. A pharmaceutical composition as claimed in claim 5 which is adapted for percutaneous administration.
- 45 9. A pharmaceutical composition as claimed in claim 8 in the form of a transdermal patch.
- 50 10. A compound of the formula:



- 35 11. A transdermal patch including a compound as claimed in claim 10
- 40 12. A soft capsule including a compound as claimed in claim 10.
- 45 13. The use of a compound consisting of a salicylate of an esterifiable organic nitrate according to claim 1 in the preparation of a medicament for the prophylaxis or treatment of angina and to achieve an anti-platelet effect.
- 50 14. The use as claimed in claim 13 wherein the esterifiable organic nitrate is indirectly esterifiable.
- 55 15. The us as claimed in claim 13 wher in the esterifiable organic nitrate is dir ctly esterifiable.
- 60 16. Th use as claimed in any of claims 13 to 15 wherein the organic nitrate compris s a compound according to any of claims 1 to 4 or 10.

Patentanspruch

1. Salicylsäureester ein organischen Nitrates, das aus folgendem ausgewählt wird: Ein in Isosorbidnitrat, ein in Glycerolnitrat, inem Pentaerythritnitrat, Mannitolhexanitrat, Trinitratphosphat, Propatinitrat und Clonitrat.

5

2. Salicylsäureester eines organisch Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Glyceroltrinitrat, Pentaerythrittrinitrat und Pentaerythrittetranitrat.

10

3. Salicylsäureester eines organischen Nitrates nach Anspruch 1, das aus folgendem ausgewählt wird: Isosorbid-2-mononitrat und Isosorbid-5-mononitrat.

4. Verbindung nach einem der Ansprüche 1 bis 3, die durch Veresterung eines veresterbaren organischen Nitrates mit Acetylsalicylsäure gebildet wird.

15

5. Pharmazeutische Zusammensetzung, die als den aktiven Bestandteil einen Salicylsäureester nach einem der Ansprüche 1 bis 4 enthält.

20

6. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur oralen Verabreichung angepaßt wird.

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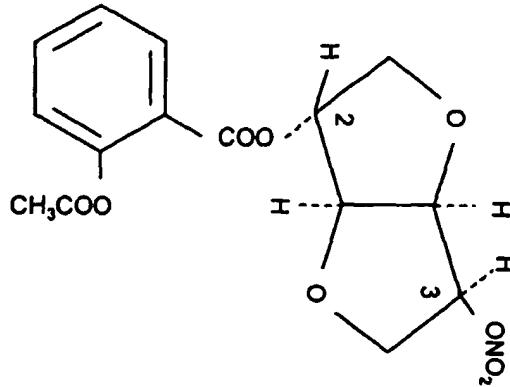
7. Pharmazeutische Zusammensetzung nach Anspruch 6 in der Form einer Tablette oder Kapsel.

8. Pharmazeutische Zusammensetzung nach Anspruch 5, die zur perkutanen Verabreichung angepaßt wird.

25

9. Pharmazeutische Zusammensetzung nach Anspruch 8 in der Form eines Transdermalpflasters.

10. Verbindung der Formel:



11. Transdermalpflaster, einschließlich einer Verbindung nach Anspruch 10.

45

12. Weichkaspel, einschließlich einer Verbindung nach Anspruch 10.

50

13. Verwendung einer Verbindung, die aus einem Salicylat eines veresterbaren organischen Nitrates nach Anspruch 1 bei der Herstellung eines Medikamentes für die Prophylaxe oder Behandlung von Angina und zur Erlangung einer Antithrombozytenwirkung besteht.

14. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat indirekt veresterbar ist.

55

15. Verwendung nach Anspruch 13, worin das veresterbare organische Nitrat direkt veresterbar ist.

16. Verwendung nach einem der Ansprüche 13 bis 15, worin das organische Nitrat eine Verbindung nach einem der Ansprüche 1 bis 4 oder 10 umfaßt.

Révendications

1. Est un salicylat d'un nitrate organique choisi parmi un nitrate d'isosorbide, un nitrate de glycéryle, un nitrate de pentaérythritol, l'mannitolhexanitrat, le phosphate de trolnitrate, le nitrate de propatyl et le clonitrate.

5 2. Est un salicylate d'un nitrate organique selon la revendication 1, choisi parmi le trinitrat de glycéryle, le trinitrat de pentaérythritol et le tétranitrate de pentaérythritol.

10 3. Ester salicylate d'un nitrate organique selon la revendication 1, choisi parmi l'isosorbide-2-mononitrate et l'isosorbide-5-mononitrate.

4. Composé selon l'une quelconque des revendications 1 à 3, formé par estérification d'un nitrate organique estérifiable avec de l'acide acétylsalicylique.

15 5. Composition pharmaceutique, contenant en tant que matière active un ester salicylate selon l'une quelconque des revendications 1 à 4.

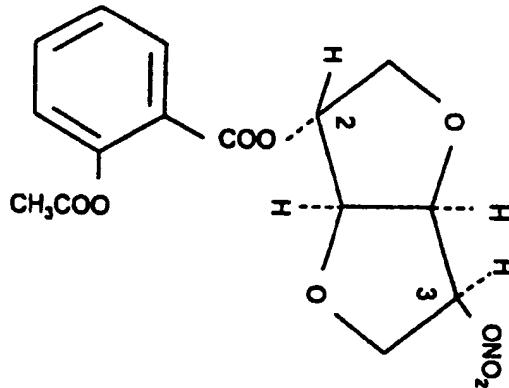
6. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration orale.

20 7. Composition pharmaceutique selon la revendication 6, sous la forme d'un cachet ou d'une gélule.

8. Composition pharmaceutique selon la revendication 5, qui est adaptée pour une administration percutanée.

9. Composition pharmaceutique selon la revendication 8, sous la forme d'un timbre transdermique.

25 10. Composé de formule :



30 11. Timbre transdermique comprenant un composé selon la revendication 10.

45 12. Gélule souple comprenant un composé selon la revendication 10.

13. Utilisation d'un composé constitué d'un salicylate d'un nitrate organique estérifiable selon la revendication 1 dans la préparation d'un médicament pour la prophylaxie ou le traitement de l'angine et pour obtenir un effet antiplaquettaire.

50 14. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable indirectement.

15. Utilisation selon la revendication 13, dans laquelle le nitrate organique estérifiable est estérifiable directement.

55 16. Utilisation selon l'une quelconque des revendications 13 à 15, dans laquelle le nitrate organique comprend un composé selon l'une quelconque des revendications 1 à 4 ou 10.

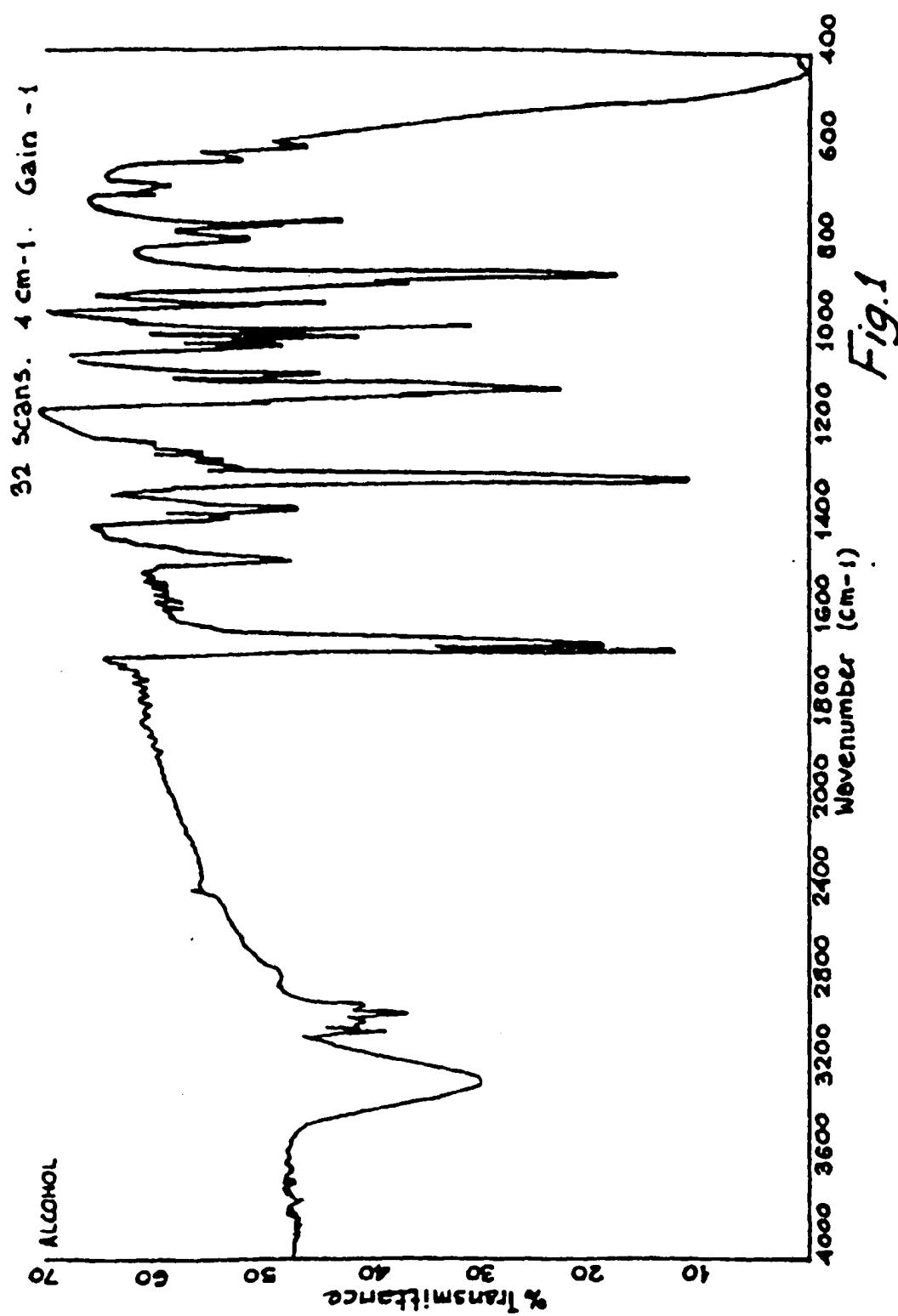


Fig.1

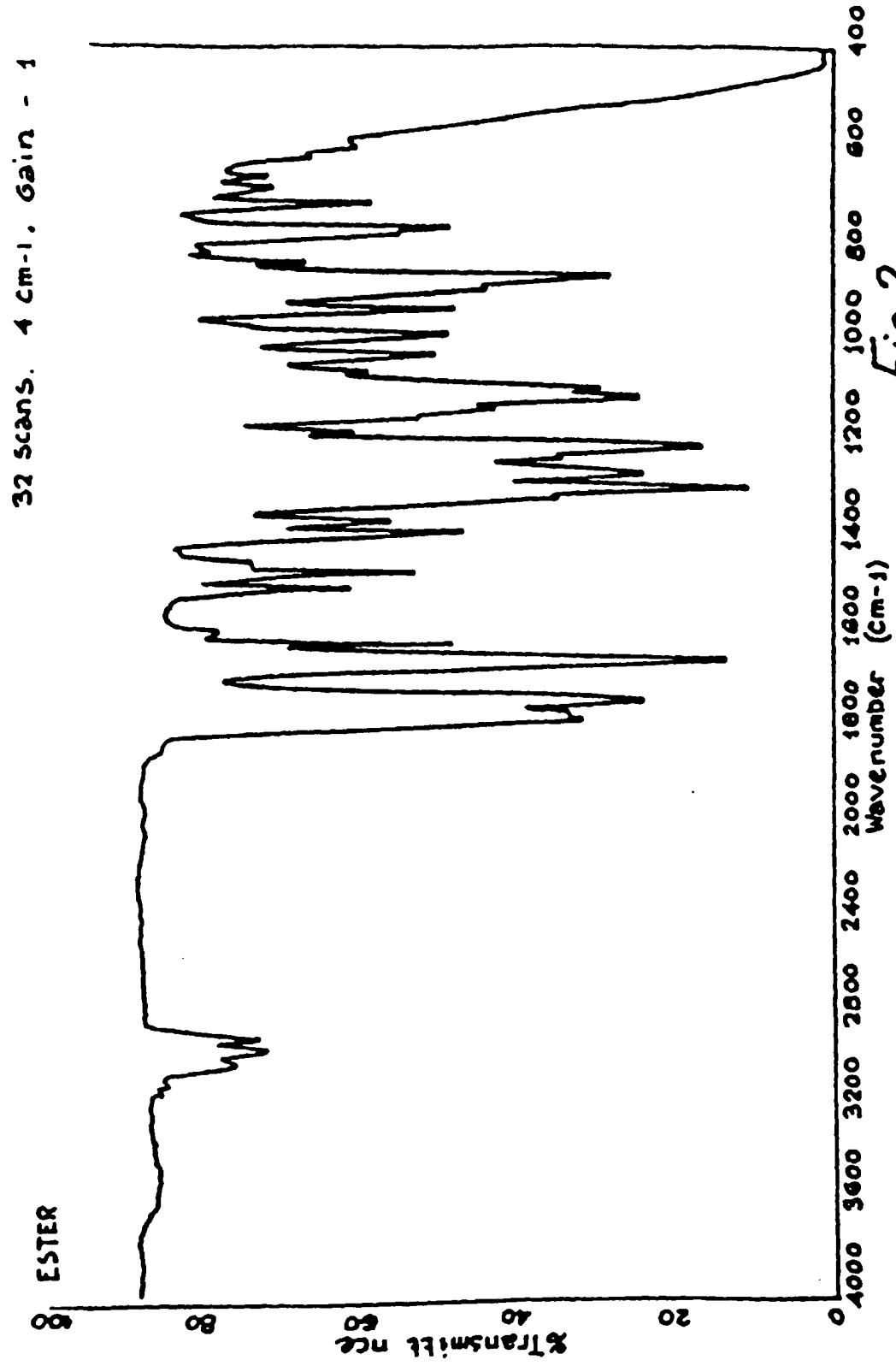


Fig. 2